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# A Comparison of Conformational Energies Calculated by Several Molecular Mechanics Methods

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## ABSTRACT

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Several commonly used molecular mechanics force fields have been tested for accuracy in conformational energy calculations. Differences in performance between the force fields are discussed for different classes of structures. MMFF93 and force fields based on the MM2 or MM3 functional form are found to perform significantly better than other force fields in the test, with average conformational energy errors around 0.5 kcal/mol. CFF91 also reaches this accuracy for the subset in which fully determined parameters are used, but it doubles the overall error due to use of estimated parameters. Harmonic force fields generally have average errors exceeding 1 kcal/mol. Factors influencing accuracy are identified and discussed. © 1996 by John Wiley & Sons, Inc.

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## Introduction

**T**he molecular mechanics method has now become a standard tool for chemists. Several

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different programs can be run on personal computers or small workstations. The problem today in routine work is not so much how to perform the calculation as what force field to use. A few years ago, two of us participated in a comparison of some of the most popular force fields at that time.<sup>1</sup> However, the last few years have seen the advent

of a plethora of new programs available on desktop computers. We have therefore updated the previous study with some of the more popular current programs.

All programs in this study have a graphics user interface for manipulating the molecules and performing the calculations. There are certainly large differences in what can be done with different packages. We have not made any attempt to grade the programs by user friendliness. This has been done elsewhere.<sup>2</sup> We have solely evaluated the accuracy that can be obtained for calculation of relative conformational energies of organic molecules. To be able to reflect normal usage, we have adhered to default settings in the programs as long as no obvious errors were introduced by this. The test set of experimental energies is essentially the same as in the previous study.<sup>1</sup> Gas phase measurements of relative enthalpies have been used whenever possible.

## Computational Methods

### MACROMODEL

Three different force fields in the program were tested: MM2\*, MM3\*, and AMBER\*. Note that these differ in several respects from the parent force fields (MM2,<sup>3</sup> MM3,<sup>4</sup> and AMBER<sup>5</sup>). Some of the differences are discussed later. MacroModel version 4.0 (ref. 6) was used. Transition states were verified by normal mode analysis. Structures were converged to a gradient of  $0.01 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$ .

### CHEM3D

Chem3D Plus version 3.1 (ref. 7) was used in this investigation. Minimizations were performed with the "MM2" force field. This implementation is based on, but not identical to, the MM2(87) force field.<sup>3</sup> The main differences lie in an extended set of parameters and the ability to include centers with more than four bonds (e.g., metals). The default convergence criterion was used (rms [root mean square] force  $0.1 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$ ).

### CERIUS<sup>2</sup>

We used version 1.5.1 of Cerius<sup>2</sup> in this work.<sup>8</sup> Three different force fields were used from this package. DREIDING 2.21<sup>9</sup> can be used for general organic and main group compounds, whereas UFF 1.01<sup>10</sup> (the Universal Force Field) is able to perform

calculations for the full periodic table. Also available as a separate module is MMFF93 (Merck Molecular Force Field).<sup>†</sup> The default convergence criterion (rms force  $0.1 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$ ) was used for all three force fields.

The DREIDING force field uses charges from the parameter file to calculate the electrostatic contributions to the total energy. Most such charges in the force field are 0. However, halides have a charge of  $-1$ . The use of these charges gives an overall negative charge of alkyl halides. To avoid this nonphysical situation, all charges were set to 0 in calculations with the DREIDING force field.

UFF is recommended for use with a conformationally dependent charge equilibrium method.<sup>11</sup> The charge updating scheme does not check for consistency at the end of an energy minimization. Thus the energy would change if, after complete minimization, the charges were recalculated. Therefore, it was necessary to calculate charges iteratively and reminimize until the energy was constant within  $0.01 \text{ kcal/mol}$ . Cerius<sup>2</sup> states that the UFF parameters were developed for use with the charge equilibrium scheme. However, in the original publication, the UFF authors say that the parametrization was done without charges.<sup>10a</sup> Therefore, UFF was also tested with all charges set to zero.

### MM2(91)

The MacMimic/MM2 package<sup>12</sup> was used. This implementation of MM2 is computationally identical to the authentic MM2(91).<sup>3</sup> The default convergence criterion was used ( $\Delta E < 0.00008 \text{ kcal/mol}$  per atom).

### ALCHEMY

Alchemy III for Macintosh (version 3.0) was used.<sup>13</sup> This program utilizes a version of the Tripos force field.<sup>14</sup> We used the default convergence criterion (rms gradient  $< 0.01 \text{ kcal/mol}$ ). Due to unreproducible results with charge calculations,<sup>‡</sup> charges were not used in any calculation. This is consistent with the method used when the Tripos force field was validated by Clark *et al.*<sup>14</sup>

<sup>†</sup>We have been unable to find any published description of this particular force field. The version in Cerius<sup>2</sup> is identical to the 1993 version in CHARMM. See ref. 57 for a more recent version of this force field.

<sup>‡</sup>Building or importing ethanol in four different ways and minimizing when charges were active resulted in energies varying by  $4 \text{ kcal/mol}$ , despite all charges and atom types being identical.

**PCMODEL**

The force field in PCModel is MMX. We used PCModel 1.0 for Windows.<sup>15</sup> This program uses an energy convergence of 0.00015 kcal/mol per atom.

**INSIGHT/ DISCOVER**

Two force fields were used from this package, CVFF (Consistent Valence Force Field) and CFF(91) (Consistent Force Field). All calculations were done with Discover version 2.95<sup>16</sup> with the complete Newton-Raphson minimizer and a convergence criterion of 0.0001 kcal mol<sup>-1</sup> Å<sup>-1</sup>. Charges were included. CVFF uses a Morse function for bond stretching, and cross terms are included in the potential functions. When creating input files through Insight, cross terms are, however, by default turned off. In all calculations reported here for the CVFF force field, cross terms were explicitly turned on. Due to major differences in the handling of charges by the two force fields, care must be taken to clear and fix all charges and potentials when shifting from one to the other.

**MM3(92)**

A Macintosh implementation of MM3(92) was used.<sup>17</sup> This implementation of MM3 is computationally identical to the authentic MM3(92).<sup>4</sup> All ground state conformations were optimized with the block diagonal minimizer. The default convergence criterion was used ( $\Delta E < 0.00008$  kcal/mol per atom). Transition state structures were calculated using full matrix Newton-Raphson optimization.

**TRANSITION STATE CALCULATIONS**

In the calculation of rotational barriers, best results can be obtained if the difference between the true transition state and the ground state can be calculated. Of the programs investigated, only MacroModel and MM3 allow optimization to a nearby transition state (the full matrix Newton-Raphson method without line search). However, all transition states in this investigation are C<sub>s</sub> symmetric in all the force fields. It was therefore possible to take advantage of the failure of most optimization methods to remove symmetry, by creating a C<sub>s</sub> symmetric structure close to the expected transition state structure and performing a normal minimization. Another possibility, which was used with PCModel in this work, is to drive

the torsion under study in increments. This method, when available, will yield rotational barriers close to the ones obtainable by true transition state optimization.

**Experimental Data**

The prime consideration in a test of empirical force fields is which molecules to use in the test set. This choice is influenced by several factors. The molecules must be chosen to reflect the area of chemistry for which the force fields are developed. Within this area, it is necessary to find test cases reflecting normal usage.

A common error in application of molecular mechanics methods is confusion of different types of energies. The large majority of experimental determinations of energy differences yield Gibb's free energies. These are often erroneously compared to the steric energies, which are the results of molecular mechanics calculations. The term *steric energy* is actually a misnomer; it is most closely related to enthalpy. In fact, steric energy differences ( $\Delta E$ ) can usually be substituted for enthalpy differences ( $\Delta H$ ) but should only be used to predict free energy differences ( $\Delta G$ ) when there is good reason to believe that the entropy difference ( $\Delta S$ ) is zero. A few methods now allow calculation of free energies from a normal mode analysis, whereas others use statistical thermodynamics to calculate free energies from extended molecular dynamics runs. However, a note of warning should be given here. These methods depend on an accurate description of the complete potential energy hypersurface, not just reliable steric energies for local minima. Of the force fields in this test, only the MM3 force fields and CFF have a functional form and parametrization that allow reliable vibrational analysis. For this reason, the test set was largely chosen from experimentally determined enthalpy differences and potential energy curves in the gas phase. Such values are extremely scarce, and in order to have a reasonable scope of the test set, a few instances of free energy values in solution had to be included. Some of these have been corrected for estimated entropy or solvation differences.

In contrast to the previous study,<sup>1</sup> only a single experimental value is considered for each system. This was necessary in order to allow statistical analysis of the data. Great care has been taken to choose the best value when multiple determina-

tions have been reported. In general, values reported for gas phase have been chosen over solution determinations, and enthalpy differences have been given precedence over the more common free energies. In the few cases in which no clear distinction could be made, the more recent value was chosen.

It is impossible to escape a certain bias when one of several possible values must be chosen. To reduce the impact of deviations in single values on the overall picture, the statistical analysis was based on average absolute errors, which are less sensitive to occasional outliers than the more commonly used terms rms (root mean square) error.

## Results and Discussion

### ROTATIONAL BARRIERS

The molecules in the test set were chosen to reflect rotational barriers for the three common types of hydrocarbon bonds,  $C_{sp^3}-C_{sp^3}$ ,  $C_{sp^3}-C_{sp^2}$ , and "single" bond  $C_{sp^2}-C_{sp^2}$ . The results are shown in Table I.

Most force fields have been parametrized to reproduce the ethane barrier as close as possible, so the good correspondence for most force fields here is not surprising. Except for UFF and Alchemy, the deviations are a few tenths of a kcal/mol. For UFF, it can be seen that the barrier was fit without charges, and then the charge model was added. This nicely demonstrates that torsional parameters should be determined after, or possibly simultaneously with, nonbonded parameters.

There is a lot more variation for the other barriers, with the largest errors for the congested isopropyl rotation in 2,4,6-trimethyl isopropyl benzene, from +6.6 kcal/mol with UFF (no charges) to -8.9 kcal/mol with Alchemy, a span of more than 15 kcal/mol.

The rotation around partial double bonds, exemplified in Table I by styrene, receives different treatment by the force fields. Alchemy and the force fields from MacroModel, Cerius<sup>2</sup>, and Insight have separate sets of parameters for  $C_{sp^2}-C_{sp^2}$  single and double bonds (and possibly special types), whereas the MM2/MM3 family (including the force fields in Chem3D and PCModel but not MacroModel) performs a  $\pi$ -calculation over the conjugated system and scales the torsional parameters according to the calculated bond order. The last method is slightly more time consuming but enables direct calculation without reparametriza-

tion of systems in which the bond order is different from standard systems (e.g., butadiene and styrene).

For the methyl rotations in both propene and isoprene, the global minimum has a methyl hydrogen eclipsed with the double bond (Fig. 1). This is reproduced by all force fields in this study, as opposed to the previous study.<sup>1</sup> The propene barrier is well reproduced by most methods but is much too low in UFF, DREIDING, and CVFF. It has been shown that the methyl rotational barrier in isoprene can be well reproduced if the torsional parameters are modified using the partial bond orders in the conjugated system.<sup>24</sup> This special treatment was used with MM2(85) in the previous study,<sup>1</sup> but it has not been included in any official MM2 release. It can be seen that most force fields calculate a too low rotational barrier. The best results are obtained by MM2\* and MMFF93, both of which use separate parameters for the  $C_{sp^2}-C_{sp^2}-C_{sp^3}-H$  torsion depending on the  $C_{sp^2}-C_{sp^2}$  bond type.

Calculations of the isopropyl rotational barrier for 2,4,6-trimethyl isopropyl benzene (Fig. 2) give large deviations from experiment for most force fields. This result might be misleading, since the experimental value here is a free energy of activation, whereas the steric energy calculated by molecular mechanics is more closely akin to enthalpy. A normal mode analysis using MM3(92) indicates that the enthalpy of activation (and thus also the steric energy of activation) is 1-2 kcal/mol lower than the free energy of activation at ambient temperature (i.e.,  $\Delta S^\ddagger \approx -5 \text{ cal mol}^{-1} \text{ K}^{-1}$ ). This seems to agree with the calculated energies from most of the force fields, but not with CVFF or the Cerius<sup>2</sup> force fields. The problem in comparing these different types of energies argues for excluding all experimental free energies from the test set, but since this is the only molecule in the set with a really congested rotation, it was still left in. Even though the real value of the activation enthalpy can be argued, it is clear that the values from Alchemy, PCModel, UFF, and DREIDING are substantially wrong.

### CONFORMATIONAL ENERGIES FOR HYDROCARBONS

Hydrocarbons are the basis of most force fields. In almost all determinations of a completely new set of parameters, the hydrocarbon parameters are determined first. The compounds in this data set are not very strained, so any reasonably well-

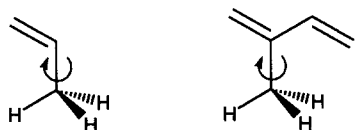
**TABLE I.**  
**Calculated Rotational Barriers in kcal/mol.**

Package Force Field Version	MacroModel			Chem3D		Cerius <sup>2</sup>				Alchemy		PCModel		Insight		MM3	Exp. <sup>a,b</sup>	Ref.
	MM2*			MM2"	MM2	UFF		UFF	No Ch. <sup>c</sup>	DREIDING	MMFF	Tripos	MMX	CVFF				
	4.0	4.0	4.0			3.1	91							1.01	2.21			
Ethane	2.7	2.4	2.8	2.7	2.7	2.7	1.9	2.9	2.9	3.2	3.8	2.7	3.1	2.6	2.4	2.878 z(A)	18	
Propene, methyl rotation	2.1	1.7	1.6	2.1	2.1	2.1	0.2	0.5	0.5	2.0	1.3	2.1	0.3	1.8	1.8	1.98 (A)	19	
Isoprene, methyl rotation	2.9	0.8	1.4	1.0	1.0	1.0	2.2	2.2	2.2	3.1	1.4	1.0	0.4	0.6	0.9	2.71 (A)	20	
Ethyl benzene, ethyl rotation	1.5	1.8	0.4	1.0	1.0	1.0	3.2	2.8	2.2	1.2	1.6	1.1	3.1	2.0	1.9	1.7 (A)	21	
2,4,6-Trimethyl isopropyl benzene, isopropyl rotation	11.0	10.9	10.4	9.9	9.5	9.5	15.7	19.4	18.1	12.8	3.9	7.2	14.8	11.2	10.0	12.8 (B)	22	
Styrene	1.7	3.3	2.4	3.3	3.3	3.3	4.5	5.2	4.8	1.0	3.5	2.9	0.4	1.5	3.8	1.78 (A)	23	

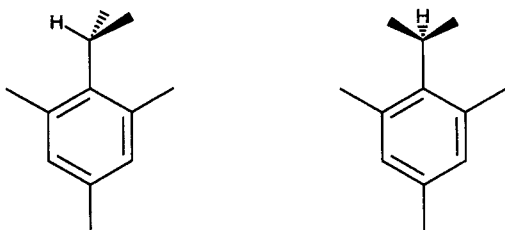
<sup>a</sup> When the experimental method is a gas phase determination of activation enthalpy or potential energy difference (method A), the number of significant digits reflects the experimental accuracy (the last digit is uncertain). For solution measurements of free energy of activation (method B), the experimental value will not correspond exactly to the optimum calculated steric energy difference.

<sup>b</sup> Measurement: A: Torsional potential energy ( $\Delta E$ ), gas phase; B: NMR, free energy of activation, solution.

<sup>c</sup> UFF 1.01 with all charges set to zero.



**FIGURE 1.** The global minima for methyl rotation in propene and isoprene. The partial double bond character of the central "single" bond of isoprene will affect the barrier in a few force fields (see text).



**FIGURE 2.** Ground state (left) and transition state ( $C_s$ , right) for isopropyl rotation in 2,4,6-trimethyl isopropyl benzene.

parametrized force field can be expected to reproduce the bond lengths and angles well. Here we are mainly testing the basic nonbonded interactions and torsional terms in the force field. The results are shown in the first three entries of Table II.

The simplest hydrocarbon that can show energetically different conformers is butane. All force fields in this study come within 1 kcal/mol of the experimental value, but UFF (with charges) and CVFF have errors exceeding 0.5 kcal/mol.

2,3-Dimethyl butane introduces some added congestion compared to the simple butane system. Like butane, this molecule tests the gauche-anti equilibrium, with a different balance between torsional preferences and nonbonded interactions. The conformational energy difference between the two forms is almost zero. This is reproduced by all force fields except DREIDING.

Steric effects are usually thought of as synonymous with crowding. However, even in the absence of solvophobic effects, van der Waals attraction can lead to stabilization if bulky groups are situated at an optimum distance from each other. This is well exemplified by 1,3,5-trineopentyl benzene, in which the most stable isomer is the one with all three groups on the same side of the ring (Fig. 3). This result is also obtained with all force fields in this study, as opposed to the preceding study.<sup>1</sup>

## CONFORMATIONAL ENERGIES OF OXYGEN-CONTAINING COMPOUNDS

Methyl acetate prefers a Z-conformation, in which the methyl group is eclipsed with the carbonyl oxygen. This is reproduced by all force fields, but the conformational energy difference between the Z and E form seems to be very hard to calculate accurately. Only four force fields come within 1 kcal/mol of the correct energy difference: MMFF93, CVFF, CFF91, and MM3(92). Most other force fields severely underestimate the energy difference, but UFF (with charges) overestimates by more than 10 kcal/mol. For UFF, it should also be noted that the charge model makes a difference of almost 16 kcal/mol. The experimental value for this energy difference does not seem to have been generally known, and therefore it is not used in parametrizations. A parametrized force field can never do better than the values put into the parametrization. It is noticeable that among the four best force fields here, we find those that depend most heavily on *ab initio* calculations in the parametrization (MMFF93 and CFF91). Among the empirically parametrized force fields, only CVFF and the recently parametrized MM3(92) fall within this group.

The situation is much better for the remaining compounds in this group. AMBER\* and all MM2/MM3-based force fields (MM2, MM2\*, MM3, MM3\*, "MM2" in Chem3D, and MMX in PCModel) do better than 1 kcal/mol. For propanol, the conformational energy difference is small. Only UFF (with charges) gives an error exceeding 1 kcal/mol. Despite this, for most force fields the small error is sufficient to return the wrong global minimum. AMBER\* is the only force field in this test that gives the correct global minimum for all oxygen-containing compounds. The eclipsing preference in butanone is reproduced by all force fields except CVFF and UFF (no charges), but it is strongly underestimated also by Alchemy. Only UFF (with charges) and CVFF give errors exceeding 1 kcal/mol for the gauche-anti difference in ethanol.

2-Methoxy-tetrahydropyran (2-methoxy-THP) is one of the common test cases for molecular mechanics force fields. The axial isomer is favored by 1 kcal/mol due to the anomeric effect (Fig. 4). The equatorial position is erroneously calculated to be most stable by UFF (both models), DREIDING, CVFF, and CFF91.

**TABLE II.**  
Conformational Energies in kcal / mol.

Package Force Field Version	MacroModel		Chem3D		Cerius <sup>2</sup>		Alchemy		PCModel		Insight		MM3	Exp. <sup>a,b</sup>	Ref.
	MM2*	MM3*	AMBER*	"MM2"	UFF	UFF	UFF	UFF	Tripos	MMX	CVFF	CFF			
	4.0	4.0	4.0	3.1	91	91	1.01	No Ch. <sup>c</sup>	93	2.21	93	91	92		
Butane, g-a	0.9	0.8	0.5	0.9	0.9	0.9	0.0	1.1	0.8	0.8	0.8	1.7	0.9	0.8	0.97 (A)
2,3-Dimethyl butane, g-a	0.1	0.4	-0.1	0.1	0.2	0.1	0.1	-0.5	-1.1	-0.4	0.2	-0.1	0.1	0.4	0.05 (A)
1,3,5-Trineopentyl benzene,	0.8	0.4	0.3	0.8	0.8	0.8	0.4	0.9	0.5	0.4	1.7	0.6	0.5	0.5	1.04 (F <sup>d</sup> )
Twosyn-allsyn															
Methyl acetate, E-Z	5.6	7.0	6.4	4.0	4.0	4.0	19.0	3.2	1.4	8.3	2.3	7.9	8.7	7.8	8 (A <sup>e</sup> )
2-Butanone, skew-ecl	1.6	1.6	1.6	1.6	1.6	1.6	1.3	-2.1	0.8	0.8	0.1	-0.4	2.3	1.4	2.0 (A)
Ethyl methyl ether, g-a	1.7	1.5	1.4	1.7	1.8	1.8	2.8	1.8	1.6	1.5	0.8	1.5	1.5	1.5	1.5 (A)
2-Methoxy-THP, eq-ax	0.5	0.9	1.4	1.1	1.2	-0.9	-1.4	-1.4	-0.2	1.5	0.4	-0.8	-1.2	0.8	1.0 (C)
Ethanol (C—O), g-a	0.6	0.4	0.2	0.6	0.6	0.6	2.2	0.5	0.1	0.1	-0.1	-1.4	0.4	0.4	0.7 (A)
Propanol (C—C), g-a	0.3	0.4	-0.2	0.3	0.3	0.3	-3.9	0.4	0.2	0.3	0.0	-1.0	0.5	0.4	-0.3 (A)
Ethyl amine (C—N), g-a	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1	-1.7	-0.7	-0.1	-0.4	0.1	0.5	-0.2	-0.1	0.7 (B)
N-Methylacetamide, E-Z	1.9	2.6	1.9	3.1	1.9	1.9	-5.1	1.7	1.4	2.5	1.1	1.0	3.1	2.9	2.4 (F)
N-Methylpiperidine, ax-eq	2.5	2.3	1.3	2.5	2.5	2.5	5.0	3.7	1.8	3.3	0.5	1.4	3.2	2.4	3.2 (C)
2-Methylpiperidine, ax-eq	2.1	2.3	1.2	2.1	2.1	2.1	4.6	3.1	1.6	2.3	1.1	2.5	2.5	2.4	2.5 (E)
3-Methylpiperidine, ax-eq	1.6	1.5	0.5	1.6	1.6	1.6	1.4	1.3	1.0	1.1	0.8	3.7	1.4	1.5	1.6 (E)
4-Methylpiperidine, ax-eq	1.7	1.7	1.1	1.7	1.7	1.7	4.2	1.8	1.3	1.3	1.4	2.4	1.8	1.8	1.93 (E)

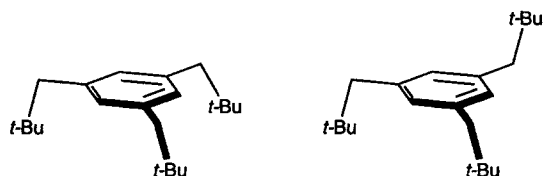
<sup>a</sup> When the experimental method is a gas phase determination of enthalpy or potential energy difference (methods A and B), the number of significant digits reflects the experimental accuracy (the last digit is uncertain). For solution measurements (low-polarity solvents only) or determinations of free energy difference (methods C–F), the experimental value will not correspond exactly to the optimal calculated steric energy.

<sup>b</sup> Measurement: A:  $\Delta H$ , gas phase; B:  $\Delta E$ , gas phase; C:  $\Delta G$ , gas phase; D:  $\Delta H$ , solution; E:  $\Delta G$ , solution, low temp.; F:  $\Delta G$ , solution.

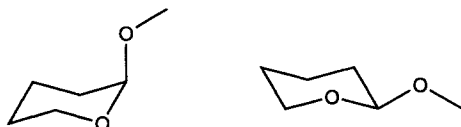
<sup>c</sup> UFF 1.01 with all charges set to zero.

<sup>d</sup> Corrected for symm. entropy ( $R \ln 3$ ), extrapolated from the 2,4,6-tribromo derivative.

<sup>e</sup> Measured by matrix trapping.



**FIGURE 3.** The two stable conformations of 1,3,5-triisopentyl benzene. The all-syn conformation (left) is the global minimum, due to attractive van der Waals forces between the *t*-butyl groups.



**FIGURE 4.** Two conformations of 2-methoxy-tetrahydropyran (2-methoxy-THP). The axial conformation (left) is the global minimum due to the anomeric effect.

### CONFORMATIONAL ENERGIES OF NITROGEN-CONTAINING COMPOUNDS

As can be seen in Table II, nitrogen is generally better treated than oxygen for the compounds in this test. UFF with charges show erratic results, but among the other force fields there are only four errors exceeding 2 kcal/mol. UFF miscalculates the gauche-anti difference in ethyl amine even in the absence of the charge model. Alchemy generally underestimates the energy of axial methyl substituents on the piperidines, especially in *N*-methylpiperidine. CVFF also mistreats the methyl piperidines, but in a more random way, whereas PCModel fails to model correctly the important peptide linkage (*N*-methyl acetamide). Most force fields actually give the wrong global minimum for ethyl amine, but the difference between the two minima is small, both experimentally and from the force fields.

### CONFORMATIONAL ENERGIES OF CYCLOHEXANE DERIVATIVES

The cyclohexane skeleton is commonly encountered in organic chemistry. It is fairly rigid, with strong 1,3-diaxial interactions. To model it accurately requires a fine tuning of the relative strengths of angular, torsional, and nonbonded interactions. To be useful to an organic chemist, a force field must be able to calculate correctly the energy difference between axial and equatorial po-

sitions for a range of substituents. The calculations on cyclohexane systems are shown in Table III.

It can be seen immediately that UFF (with charges) and CVFF seriously overestimate the axial energy for all substituents and the energy of the twist-boat cyclohexane conformation. The balance between rigidity and nonbonded interactions has failed for these force fields. For UFF, it can be seen easily that the main fault lies with the charge model, because the results are much improved when no charges are used in the calculations.

The twist-boat energy is also overestimated by more than 2 kcal/mol by DREIDING, Alchemy, and CFF91. Axial energies are generally underestimated by AMBER\*, DREIDING, and MMFF93. An exception is phenyl cyclohexane, for which the axial energy is overestimated by all force fields except AMBER\* and Alchemy.

The amino group is only treated correctly by the MM2/MM3-based force fields. On the other hand, the axial energy excess of dimethylamino cyclohexane is calculated within a few tenths of a kcal/mol by most force fields (except for the previously mentioned UFF with charges and CVFF).

### CONFORMATIONAL ENERGIES OF HALOALKANES

From a molecular mechanics standpoint, halides differ from other heteroatoms in several respects. The number of new parameters required to do calculations on an alkyl halide is lower than the number of parameters needed to introduce a non-terminal heteroatom (e.g., an amine nitrogen or an ether oxygen). On the other hand, the electronegativity of the halides introduces strong electrostatic forces, something that upsets many otherwise well-behaved force fields. Fluorine, in particular, will also participate in sacrificial hyperconjugation and similar phenomena, which complicates especially the determination of torsional parameters. In many cases, parameters for the halides seem to have been of secondary importance for the force field developers. The results of the alkyl halide calculations are shown in Table IV.

Some force fields require extra notice. The default for the DREIDING force field is to put a charge of  $-1$  on any halogen atom. Since no other atom types used in this test set are treated as charged, this gives an overall negative charge to alkyl halides. To avoid this nonphysical situation, all charges were zeroed in the DREIDING calculations. CFF91 does not contain finalized parameters



**TABLE III.**  
Conformational Energies of Cyclohexanes, in kcal/mol.

Package	MacroModel			Chem3D		Cerius <sup>2</sup>				Alchemy		PCModel		Insight		MM3	Exp. <sup>a,b</sup>	Ref.
	Force Field			MM2		UFF				Tripos		MMX		CVFF				
	MM2*	MM3*	AMBER*	MM2"	UFF	UFF	No Ch. <sup>c</sup>	DREIDING	MMFF	Tripos	MMX	CVFF	CFF					
Version	4.0	4.0	4.0	3.1	91	1.01	2.21		93	3.0	1.0	91	92					
Cyclohexane, twb-ch	5.4	6.5	5.8	5.4	5.4	9.6	8.8	7.7	6.4	7.7	7.7	5.4	5.4	10.6	7.5	5.8	5.5 (A <sup>d</sup> )	37
Phenylcyclohexane, ax-eq	3.9	4.3	2.0	3.6	3.6	7.9	6.3	4.5	3.3	2.5	2.5	3.5	3.5	4.5	4.2	4.2	2.87 (F)	38
Methylcyclohexane, ax-eq	1.8	1.8	1.0	1.8	1.8	3.5	1.9	1.3	1.4	1.4	1.4	1.8	1.8	3.0	1.8	1.8	1.75 (D)	39
Aminocyclohexane, ax-eq	1.4	1.2	-0.3	1.4	1.4	3.8	0.8	0.5	0.8	0.0	0.0	1.4	1.4	3.4	0.4	1.2	1.49 (E)	40
N,N-Dimethylamino-cyclohexane, ax-eq	1.0	1.2	1.2	1.0	1.0	5.2	2.0	0.6	0.5	1.5	1.5	1.0	1.0	6.2	1.0	1.1	1.31 (E)	40
trans-1,2-Dimethyl-cyclohexane, ax, ax-eq, eq	2.4	2.6	1.3	2.4	2.4	5.4	1.9	1.3	1.5	2.0	2.0	2.4	2.4	4.0	2.7	2.6	2.58 (E)	41
cis-1,3-Dimethyl-cyclohexane, ax, ax-eq, eq	5.3	5.7	4.4	5.3	5.3	11.8	6.7	4.7	4.8	5.2	5.2	5.3	5.3	7.5	5.4	5.7	5.5 (A <sup>e</sup> )	42

<sup>a-c</sup> See Table II.

<sup>d</sup> Measured by matrix trapping.

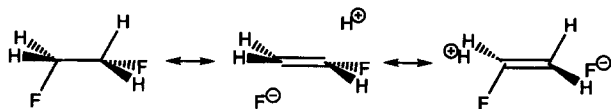
<sup>e</sup> Extrapolated from 1, 1, 3, 5-tetramethylcyclohexane.

**TABLE IV.**  
Conformational Energies of Haloalkanes, in kcal/mol.

Package Force Field Version	MacroModel		Chem3D		Cerius <sup>2</sup>		Alchemy		PCModel		Insight		MM3	Exp. <sup>a,b</sup>	Ref.
	MM2*	MM3*	AMBER*	"MM2"	MM2	UFF	UFF	UFF	UFF	UFF	UFF	UFF	UFF		
	4.0	4.0	4.0	3.1	91	1.01	No Ch. <sup>c</sup>	2.21	93	MMFF	Tripos	MMX	CVFF	91	92
FCH <sub>2</sub> CH <sub>2</sub> F, g-a	-0.6	-0.6	0.8	-0.6	-0.6	- <sup>d</sup>	0.1	0.1	-0.6	0.0	0.0	0.0	3.6	4.2	-0.6
PrCl, g-a	0.2	0.3	0.2	0.2	0.2	-3.7	0.8	0.5	0.0	0.1	0.1	0.2	1.5	1.2	-0.36 (A)
ClCH <sub>2</sub> CH <sub>2</sub> Cl, g-a	0.4	1.4	0.7	1.6	1.6	6.7	0.6	0.4	1.3	0.0	0.0	1.7	2.8	2.7	1.7
ClCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl, g, a-g, g	0.3	0.0	-0.2	0.0	0.0	-1.2	-0.8	-0.5	0.4	0.1	0.1	0.1	0.1	0.3	0.0
ClCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl, a, a-g, g	0.8	0.2	-0.1	0.1	0.1	-0.8	-1.6	-1.0	1.1	0.0	0.0	0.4	0.0	0.3	0.1
															1.5 (A)

<sup>a-c</sup> See Table II.

<sup>d</sup> The gauche conformation was not recognized as an energy minimum by UFF. No penalty was applied in the average error calculation (cf. Table VII).



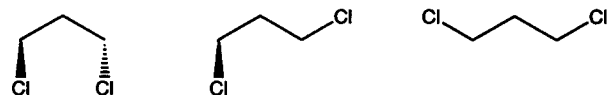
**FIGURE 5.** Sacrificial hyperconjugation in 1,2-difluoroethane.

for the halides. The calculations are run with estimated parameters, with a warning given in the log file.

1,2-Difluoroethane is one of the systems in which sacrificial hyperconjugation is most apparent (Fig. 5). The fluorines prefer a dihedral F—C—C—F angle close to 90°, thus avoiding overlap with the same *p* orbitals on the C—C system. This gauche conformation is favored over the anti conformation by 0.8 kcal/mol. This is well reproduced by the MM2/MM3-based force fields, except PCModel, which is based on a version of MM2 that was parametrized before the magnitude of this effect had been recognized. MMFF93 also treats this compound very well. The remaining force fields predict the anti isomer to be most stable. In UFF, use of charges results in a repulsion of such magnitude that the gauche conformation is no longer recognized as even a local minimum. CVFF and CFF91 give errors of 4–5 kcal/mol.

All force fields except UFF with charges give the wrong global minimum for propyl chloride. The same erroneous result was obtained for all force fields in the previous study.<sup>1</sup> On the other hand, UFF has by far the largest absolute error for this compound. OnlyAlchemy fails to return the anti conformation of 1,2-dichloroethane as the global minimum. Here CVFF and CFF91 overestimate the energy difference by more than 1 kcal/mol, but UFF with the charge model overestimates by almost 6 kcal/mol.

The gauche–gauche conformation of 1,3-dichloropropane is experimentally the most stable one (Fig. 6). No force field reproduces the correct stabi-



**FIGURE 6.** Three low-energy conformations of 1,3-dichloropropane. The gauche–gauche conformation (left) is most stable. Another gauche–gauche conformation with two parallel C—Cl bonds has a very high energy.

lization of this particular conformer, and several [AMBER\*, Chem3D, MM2(91), UFF, and DREIDING] calculate another global minimum.

## CONFORMATIONAL ENERGIES OF HALOCYCLOHEXANES

Also for halides, the substituted cyclohexanes are treated separately from the rest of the compounds. The results are shown in Table V. Compared to the previous study, several halogenated compounds were removed from the data set, to avoid a too strong bias of the investigation toward the halide systems. The compounds removed were those for which experimental data were least reliable or missing.

Alchemy will use some programmed parameter for any bond, irrespective of whether it has been explicitly parametrized. This was especially noticeable for the bromides, in which the carbon–bromine bond was treated as carbon hydrogen. No warnings are given about these parameter substitutions. This is dangerous and can easily lead to meaningless results unless each single parameter is checked for each system.

It can be seen that halides experimentally have a fairly small bias toward the equatorial position. For all dihalides except 1,2-difluoro, the diaxial conformation is in fact the global minimum. It has been shown that the axial bias of the dihalides can be rationalized by favorable electrostatic interaction between the negative charge of one halide and positive charges induced by the other halide (Fig. 7).<sup>53</sup> Most force fields treat the hydrogens as uncharged and thus fail to reproduce the correct stabilization of the axial position.

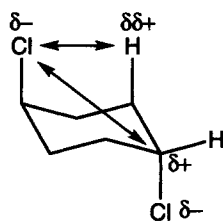
Errors are generally larger in these rigid systems than in the flexible haloalkanes discussed earlier. The results vary substantially between the force fields. The large errors from the UFF force field can again be traced to an exaggerated electrostatic interaction, but even without the charge model, UFF shows large errors for the dihalocyclohexanes. CVFF and CFF91 consistently give much too large axial energies, possibly due to excessive van der Waals interactions, but in the case of CFF91 also due to low quality parameters (*vide infra*). Most other force fields also overestimate the axial energies, especially for the last entries in Table V. MMFF93, on the other hand, gives a good result but systematically underestimates the axial energies slightly.

**TABLE V.**  
**Conformational Energies of Halocyclohexanes, in kcal / mol.**

Package	MacroModel			Chem3D "MM2"	Cerius <sup>2</sup>				Alchemy		PCModel	Insight		MM3	Exp. <sup>a,b</sup>	Ref.		
	MM2*		MM3*		AMBER*	UFF	UFF	No Ch. <sup>c</sup>	DREIDING	MMFF		Tripos	MMX				CVFF	CFF
	4.0	4.0	4.0		4.0													
Force Field																		
Version					3.1	91	1.01	2.21	93	3.0	1.0			91	92			
F, ax-eq	0.2	0.2	0.3	*	0.2	0.2	4.1	0.4	0.3	0.0	0.2	2.8	2.0	0.2	0.16 (A)	47		
Cl, ax-eq	0.4	0.6	0.5		0.4	0.4	2.8	1.2	0.8	0.1	0.4	2.5	2.0	0.6	0.5 (A)	48		
Br, ax-eq	0.5	0.6	0.8		0.5	0.5	2.5	1.3	0.5	0.1	0.5	2.5	2.0	0.7	0.7 (A)	49		
trans-1,2-diF,	0.8	0.9	-0.3		0.8	0.9	-9.6	0.7	0.6	-0.1	0.0	1.8	0.8	0.9	0.59 (D <sup>d</sup> )	50		
ax, ax-eq, eq																		
trans-1,2-diCl,	0.9	-0.4	0.1		-0.9	-0.9	-9.7	1.7	1.2	0.4	-0.9	1.9	1.2	-0.6	-0.93 (A)	51		
ax, ax-eq, eq																		
trans-1,2-diBr,	-0.7	-0.4	0.7		-0.9	-0.9	-6.7	1.6	0.9	-4.3	-0.9	2.3	1.7	-0.6	-1.5 (D <sup>d</sup> )	51		
ax, ax-eq, eq																		
trans-1,4-diF,	-0.5	-0.3	-0.2		-0.4	-0.4	-5.1	0.8	0.7	-0.1	-0.5	3.8	2.5	-0.2	-1.14 (F <sup>d</sup> )	52		
ax, ax-eq, eq																		
trans-1,4-diCl,	0.3	0.7	0.1		0.5	0.5	-4.4	2.4	1.7	0.4	0.3	3.4	2.7	0.8	-0.8 (D <sup>d</sup> )	51		
ax, ax-eq, eq																		
trans-1,4-diBr,	0.6	0.9	1.2		0.7	0.8	-2.2	2.6	1.0	0.4	0.6	3.9	3.1	1.1	-0.88 (D <sup>d</sup> )	51		
ax, ax-eq, eq																		

<sup>a-c</sup> See Table II.

<sup>d</sup> The value shown is extrapolated to gas phase.



**FIGURE 7.** Electrostatic attractions in dihalocyclohexanes, stabilizing the diaxial conformation.

### CONFORMATIONAL ENERGIES OF CONJUGATED COMPOUNDS

The treatment of conjugated systems differs substantially between different force fields. The differences can be divided into two parts: how the bond orders are estimated, and how the bond order affects the calculated steric energy.

The simplest approach to the first problem is to require the user to input a bond type, which could be a simple type (like single, double, and triple) but also a more complex type (like aromatic or amide). The latter types are usually recognized automatically by the program from the environment of the bond. A more complex approach, used by the MM2/MM3 family (Chem3D, MM2, PCModel, and MM3), is to calculate fractional bond orders using quantum chemical methods.

The bond orders can affect the energies in two different ways. Programs like MacroModel keep separate parameters for each distinct possible bond type. This cannot be done if fractional bond orders are used. Instead, a function must be defined which calculates parameters from estimated bond orders.

Two examples of conjugated compounds that can be expected to work in any force field are shown in Table VI. Here we are mainly testing the energies at the two extremes of the torsional potential. Related to these systems is the rotational barrier of styrene shown in Table I.

The situation for both these compounds has been improved dramatically from the previous study, but Alchemy and CVFF still show errors larger than 1 kcal/mol for butadiene. DREIDING and again Alchemy give errors exceeding 1 kcal/mol for acrolein, whereas UFF with charges gives an error more than twice as large as any other force field and predicts the *s-cis* conformer to be the global minimum. This can be attributed to a strong electrostatic attraction between the oxygen and one  $\beta$ -hydrogen, as again UFF without charges gives a reasonable result.

### COMPARING THE FORCE FIELDS

The mean absolute errors from each table are shown in Table VII and graphically in Figure 8. This robust measure of accuracy was chosen over the more sensitive rms errors due to the presence of some potential outliers (e.g., 2, 4, 6-trimethyl isopropyl benzene, Table I). For comparison, the overall best force field from the previous test, a slightly modified version of MM2(85),<sup>24</sup> is also included. The last set of data correspond to blank values—that is, errors from setting all energy differences to 0 kcal/mol. The total height of a bar in Figure 8 is not exactly proportional to the overall error for the test set. Each section of a bar is directly proportional to the mean absolute error from one group of data. Since the groups have unequal weights due to the differing number of data points, the total height will only be approximately proportional to the overall mean error. The proportionality factor varies in the range 6.6–7.9. We believe that the display in Figure 8 gives a good picture of the general applicability of a force field. All force fields have been tested pairwise for statistically significant differences in accuracy. This has been done by comparing paired residuals between experimental and calculated energies by a Student's *t* test.<sup>8</sup> Differences with a confidence level under 80% are considered insignificant.

Looking at the total picture, it can be seen that MMFF93 and the complete range of MM2/MM3-based force fields give acceptable accuracy over the entire data set. Differences within this group have a low significance, but pairwise tests between this group and the remaining force fields in all cases gave significant differences at a confidence level exceeding 90%. The charge model in UFF must be considered unsuitable for energetic calculations of organic molecules. The remaining force fields should be used with caution and, if possible, validated for each specific class of compounds in which energetic predictions are to be performed.

<sup>8</sup>All statistical calculations were performed with Microsoft Excel 4.0 running on a Macintosh Quadra 800. The methods employed were taken from the manuals to the program and from the following references: D. G. Kleinbaum, L. L. Kupper, and K. E. Muller *Applied Regression Analysis and Other Multivariate methods*, PWS-KENT Publishing Company, 20 Park Plaza, Boston, MA 02116. W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, *Numerical Recipes in C*, Cambridge University Press, The Pitt Building, Trumpington Street, Cambridge, UK, CB2 1RP.

**TABLE VI.**  
**Conformational Energies of Conjugated Compounds, in kcal / mol.**

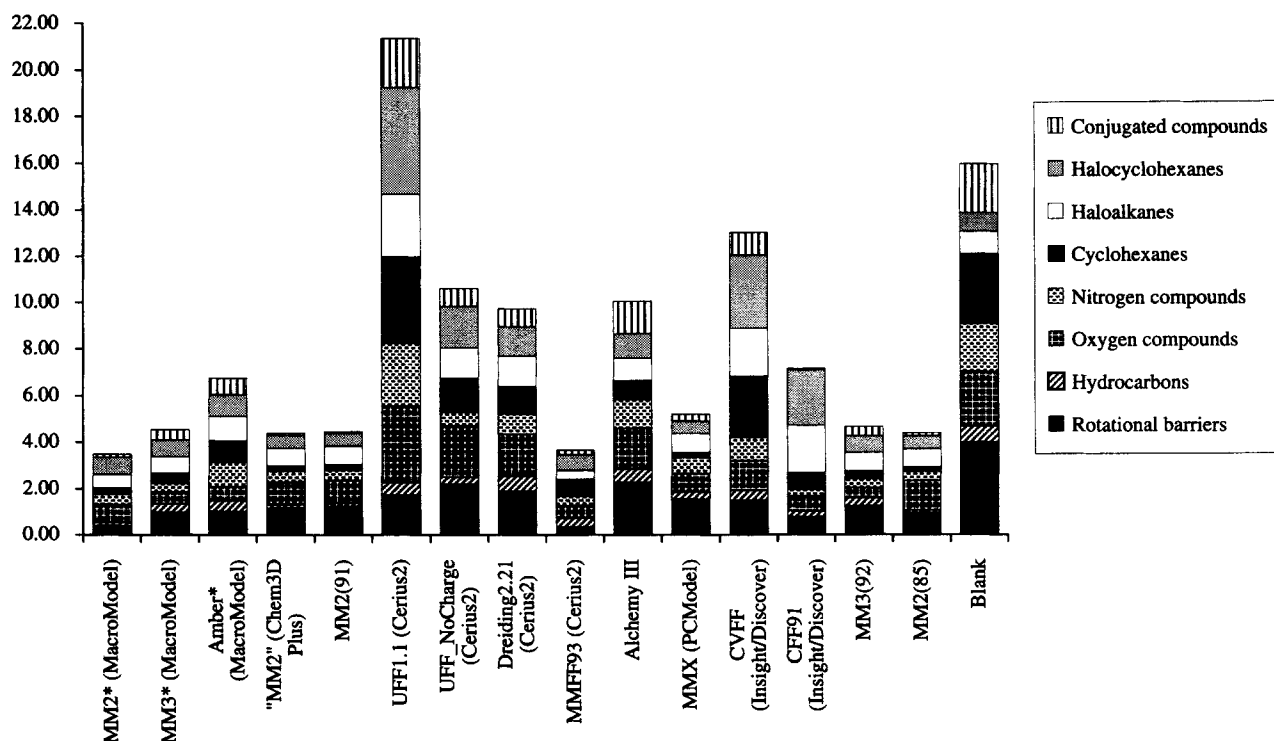
Package Force Field Version	MacroModel		Chem3D "MM2"	MM2		Cerius <sup>2</sup>			Alchemy		PCModel		Insight		MM3	Exp. <sup>a,b</sup>	Ref.
	MM2*	MM3*	AMBER*	UFF	UFF	UFF	DREIDING	MMFF	Tripos	MMX	CVFF	CFF					
	4.0	4.0	4.0	1.01	3.3	3.5	2.21	93	3.0	1.0	91	91			92		
Butadiene, s-cis – s-trans	2.7	1.7	3.2	2.3	2.3	3.5	2.0	2.5	1.3	2.2	4.4	2.5	1.9	2.5 (B)	54		
Acrolein, s-cis – s-trans	1.6	1.9	2.4	1.6	1.7	1.1	0.6	2.0	0.1	1.4	1.8	1.6	1.5	1.7 (A)	55		

<sup>a-c</sup> See Table II.

**TABLE VII.**  
Average Absolute Errors, in kcal/mol.

Package Force Field Version	MacroModel			Chem3D "MM2"	MM2	Cerius <sup>2</sup>				Alchemy		PCModel	Insight		MM3	MM2	Blank	
	MM2*	MM3*	AMBER*			UFF	UFF	No Ch. <sup>a</sup>	DREIDING	MMFF	Tripos		MMX	CVFF				CFF
	4.0	4.0	4.0	3.1	91	1.01	1.72	2.21	1.91	0.35	2.27	1.55	1.50	0.79	1.25	0.95	3.97	
Rotational barriers	0.41	1.00	1.02	1.18	1.25	1.72	2.21	2.21	1.91	0.35	2.27	1.55	1.50	0.79	1.25	0.95	3.97	
Hydrocarbons	0.14	0.36	0.48	0.14	0.14	0.56	0.30	0.30	0.65	0.39	0.57	0.29	0.42	0.24	0.35	0.12	0.69	
Oxygen compounds	0.79	0.50	0.59	0.99	1.00	3.27	2.18	2.18	1.78	0.52	1.75	0.80	1.28	0.65	0.42	1.28	2.34	
Nitrogen compounds	0.42	0.38	1.06	0.45	0.42	2.70	0.60	0.60	0.88	0.43	1.23	0.68	1.00	0.31	0.40	0.38	2.05	
Cyclohexanes	0.28	0.43	0.89	0.24	0.23	3.71	1.44	1.44	1.15	0.71	0.80	0.22	2.60	0.71	0.34	0.21	3.00	
Haloalkanes	0.59	0.72	1.07	0.76	0.79	2.70	1.32	1.32	1.31	0.39	0.97	0.82	2.09	2.02	0.80	0.76	0.96	
Halocyclohexanes	0.72	0.69	0.93	0.53	0.55	4.57	1.78	1.78	1.26	0.68	1.05	0.53	3.13	2.36	0.69	0.54	0.80	
Conjugated compounds	0.15	0.46	0.70	0.11	0.08	2.11	0.79	0.79	0.80	0.19	1.42	0.30	0.98	0.08	0.40	0.15	2.10	
Total	0.50	0.60	0.88	0.60	0.62	3.01	1.48	1.48	1.29	0.51	1.27	0.68	1.88	1.08	0.61	0.60	2.03	
Excluding Table I	0.51	0.53	0.86	0.51	0.52	3.22	1.36	1.36	1.20	0.53	1.11	0.55	1.94	1.13	0.51	0.55	1.73	

<sup>a</sup> UFF 1.01 with all charges set to zero.



**FIGURE 8.** Errors of the different methods. The height of each field in a bar is proportional to the average absolute error for one table. Thus, the total height of each bar is only approximately proportional to the total error in Table VII. The proportionality factor varies between 6.6 and 7.9.

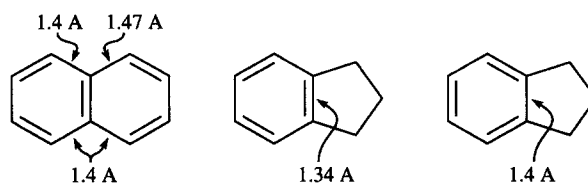
## Force Field Details

### MACROMODEL FORCE FIELDS

The MacroModel program was the first successful application of a now increasingly popular concept: building a generalized force field shell within which other force fields can be mimicked. For each structural element, the user has a choice between several functional forms (e.g., for bond stretch, the function can be simple harmonic or include higher order terms). Some restrictions are imposed by the shell, making it impossible to get exact correspondence between the original force fields and the local implementations.

MacroModule includes an extensive system for recognizing specific substructures in molecules. The recognition system is flexible but includes pitfalls for the novice user. Since a specific structural element (e.g., a C—C bond) can be recognized by several different substructures in the force field, the results may depend both on the ordering of the substructures in the force field file and the numbering of atoms in the structures. For exam-

ple, in a calculation of naphthalene using the MM3\* force field, the identical bonds to the bridgehead carbons were identified differently, yielding reference bond lengths that differed by 0.07 Å (Fig. 9). MM3\* also yields different results for the different Kekulé forms of indane (Fig. 9). Therefore, care is recommended when using MacroModel. Even experienced users can easily be surprised by which parameters are used in each specific case. However, when the problems were recognized, both of the aforementioned situations could easily be amended by removal of selected parts of the force field substructure section. When the pitfalls are avoided, all of the MacroModel force fields give good results.



**FIGURE 9.** Discrepancies in the MM3\* force field due to limitations in the substructure recognition.



**MM2\***

The implementation of MM2\* included some drastic changes from the parent force field MM2(87).<sup>||</sup> The electrostatic treatment in MM2 consists of dipole interactions. MM2\* instead uses charge-charge interaction with a distance-dependent dielectric constant as default, with atom point charges calculated from the MM2 bond dipoles. The difference is most important when selection rules in MacroModel exclude part of the electrostatic interaction present in MM2. When two bonds with strong dipoles are connected by a common bond (e.g., vicinal dihalides, acetals, or esters), only one of the four charge-charge interactions that are supposed to replace the single dipole-dipole interaction is actually included in the energy expression. When one more bond is intervening, one of the four interactions is still excluded. This treatment is not *a priori* better or worse than the treatment in MM2, but the interplay with other interactions will surely be affected and the parameters have largely been adopted from MM2 without modification. It can be seen that the largest differences between MM2\* and MM2(91) can be found for compounds incorporating close, strongly electronegative atoms. Interestingly, despite the fact that the parameters were developed for the MM2 functional form, in some cases (e.g., methyl acetate, 1,3-dichloropropane) MM2\* does a better job than MM2(91).

The  $\pi$ -system calculation in MM2 has been removed in MM2\*. Instead, MM2\* utilizes user-input bond order specifications to differentiate between, for example, conjugated single bonds and double bonds. This allows correct treatment of, for example, dienes. The substructure feature is used to recognize some conjugated systems (e.g., benzene) and apply special parameters. The test set includes no molecules for which MM2\* lacks specific parameters. A wide range of monocyclic heterocyclic systems and other conjugated systems are recognized by MM2\*, but it is still wise to check what parameters are actually used in any calculation including conjugated systems. No long-range effects from, for example,  $\pi$ -active benzene substituents are recognized by MM2\*. Hydrogen bonding in MM2\* has been modeled after AMBER, not MM2. However, these changes should not affect any of the molecules in the test set.

Despite the extensive use of unmodified MM2 parameters with a different functional form, MM2\*

<sup>||</sup> For the compounds in this test, MM2(87) give results that are essentially identical to MM2(91).

does significantly better than MM2(91) for the test set, to a confidence level of > 90%. As can be seen from Table VII, this is entirely due to an improved accuracy for calculation of rotation barriers. A closer analysis reveals that MM2\* has a more flexible parameter set for alkyl groups attached to a conjugated system. For conformational energies, the accuracies of MM2\* and MM2 are virtually identical (last row, Table VII).

**MM3\***

MM3\* is derived from MM3(89)<sup>†</sup> in a manner analogous to the creation of the MM2\* force field from MM2(87), with parameters updated through 1991. All differences listed for MM2\* also apply to MM3\*. The number of recognized substructures is much lower in MM3\* than in MM2\*. For example, pyridine is treated as a series of isolated single and double bonds. However, for the test set, the recognition systems in MM2\* and MM3\* were equally efficient. MM3(92) tested in this work has been improved significantly compared to the version used in the development of MM3\*, MM3(89). Despite this, MM3 and MM3\* give the same overall accuracy.

**AMBER\***

No official version of AMBER has been tested with the present data set. However, the deviations from the original functional form are much smaller for AMBER\* than for MM2\* and MM3\*. AMBER\* can be set to mimic different versions of AMBER. The default in AMBER\* is to use a distance-dependent dielectric constant with charges assigned from substructure recognition and bond dipoles in a way that exactly reproduces the united atom AMBER charges (note that AMBER\* still defaults to an all-atom force field). AMBER\* is a purely diagonal, harmonic force field, containing no cross terms (e.g., stretch-bend interactions).

AMBER\* is more successful than the other major harmonic force fields in this test (DREIDING and Alchemy), to a significance level of better than 97%. The most probable source of this difference can be found in the treatment of charges. For different reasons, charges could not be used with either DREIDING or Alchemy. The assignment of charges from substructures in AMBER\* sometimes

<sup>†</sup>Substantial changes have occurred between MM3(89), which is the basis for MM3\*, and MM3(92), which is tested in this work. However, for the compounds in the test set, the differences are probably minor.

will yield incorrect total charges (e.g., nucleotides). It is also possible that the success of AMBER\* represents a more careful parametrization than for the other harmonic force fields.

### CHEM3D AND MM2

There is a close correspondence between values calculated by "MM2" in Chem3D and MM2(91). This is not surprising, since Chem3D "MM2" is based on the MM2(87) force field with very few modifications relevant to the molecules in the test set. The only two energy differences exceeding 0.1 kcal/mol are for methyl acetamide and trimethyl isopropyl benzene.

The MM2(85) force field used in the previous study was specially modified to account for the fractional bond order of the conjugated system also when calculating the torsional potential for rotation of attached alkyl groups. In this study only the rotational barrier for isoprene is affected, but the difference is larger than 1 kcal/mol. Due to parameter changes, the value for methyl acetate has been improved by more than 1 kcal/mol in the newer version. It can be seen that MM2(85) and MM2(91) agree at the points at which there were differences between Chem3D "MM2" and MM2(91). The changes in Chem3D therefore cannot be attributed to the derivation from an older force field, but rather to parameter substitutions.

Changes in the MM2 force field in Chem3D outside the scope of this test include several added parameters and the ability to calculate multicoordinated centers (e.g., metal complexes).

### UFF

UFF without charges is comparable in accuracy to, for example, DREIDING. When the recommended charge model is added, it is the only force field in the test that does significantly worse than the blank test. At the current level of development, it cannot be used for predictions about energy differences. Despite this, it is an interesting force field. UFF tries to address the problem of the arithmetic explosion of required parameters in most force fields. The developers have tried to find a functional form in which the parameters can be calculated from a small programmed set of basic properties. This new approach is still at an early stage of development and cannot be expected to perform as well as force fields that have seen decades of continuous improvement. When this force field reaches an acceptable level of accuracy,

it has a wide scope. As the only force field in this test, it can perform calculations over the entire periodic table. However, because complexes including metals often display strong charge separation, the bad performance of UFF including the charge model is of considerable concern.

### DREIDING

DREIDING, as implemented in Cerius<sup>2</sup>, is a purely diagonal, harmonic force field with rudimentary electrostatic treatment. More elaborate versions of DREIDING exist.<sup>9</sup> For reasons given earlier, the only electrostatic interactions that would have been calculated in the test set, repulsion between two halides, were set to zero. DREIDING can be used with charges derived from different sources (e.g., quantum chemical calculations),<sup>9</sup> something that could well improve the performance of this force field. Cerius<sup>2</sup> does include different schemes for assigning charges. However, none seems to have been validated for use with DREIDING.

Most harmonic force fields, both in the previous and the current study, give similar accuracies. The singular exception is AMBER\*. Interestingly, two of the most commonly used semiempirical quantum chemical methods (AM1 and PM3, tested in the previous study<sup>1</sup>) give accuracies similar to harmonic force fields. It is strongly recommended that calculations with harmonic force fields or semiempirical methods are validated for the class of compounds under study.

### MMFF93

We have been unable to find a published description of this version of MMFF; therefore, a short summary of the part of the force field relevant to this study will be given here. MMFF93 employs a quartic stretch function and a cubic bend function. Out-of-plane bendings are described by an angle between one bond and the plane defined by the central atom and the two other substituents. For torsions, the threefold representation used in MM2 and MM3 is utilized. The special "buffered 14-7" form of the van der Waals function has been published.<sup>56</sup> Electrostatic interactions use a buffered form with fractional point charges constructed from a basic charge modified by bond polarity. The only cross term in MMFF93 is a stretch-bend interaction. The parametrization is, to a large extent, based on *ab initio* calculations, basically at the MP2/6-31G\* level but in many

cases employing larger basis sets and/or higher correlation methods.

As can be seen from Figure 8, MMFF93 is one of the best force fields in this test. The difference between MMFF93 and MM2/MM3-based force fields is in no case statistically significant, but it is better than the remaining force fields at a confidence level exceeding 99%. It is an all-purpose force field, with no group of compounds in this test being worse than any other.

### ALCHEMY

Alchemy is the personal computer version of the Tripos force field. This is a purely diagonal, harmonic force field developed primarily for calculation of structures of macromolecules. The overall result is very similar to the DREIDING force field, as well as to the harmonic force fields and semiempirical methods in the previous study.<sup>1</sup> As for DREIDING, no charges could be used in the calculations, but for different reasons. Because the force field was validated without using charges,<sup>14</sup> this was felt to be the appropriate mode for running the program. However, the inability to use charges must be considered a serious flaw in the program.

The conclusions drawn for the DREIDING force field are valid also for Alchemy. The errors are fairly evenly distributed but seem to be proportionally larger in strained states.

### PCMODEL

The internal force field in PCModel, called MMX, is based on the first public version of MM2 (1977)<sup>3</sup> but has been substantially developed since. It can be classified into the MM2 family. It seems to do slightly worse than the rest of the family, but in general only with about 80% confidence level. Outside the MM2/MM3-based force fields, PCModel is better than any except MMFF93, with at least 94% confidence. PCModel includes several features not present in MM2, especially in the field of metal complexes.

### INSIGHT/ DISCOVER

Both CVFF and CFF91 are nondiagonal force fields, containing several types of cross terms. However, CVFF was originally a diagonal force field which has been enhanced in later developments, whereas CFF91 from the start has been developed as a highly nondiagonal force field.

Both have the increasingly common ability to use general parameters when no explicit parameters are available. For the compounds in the test set, CVFF has a much higher proportion of explicit parameters than CFF91. For example, for the halides (Table IV) all diagonal terms were available explicitly for CVFF, whereas in some cases CFF91 had to assign about half the diagonal terms from general parameters.

From the summary in Figure 8, it can be seen that the attempt to enhance CVFF to the accuracy of most other nondiagonal force fields has failed. Indeed, CVFF gives a worse result than all standard diagonal force fields (UFF excepted). The use of CVFF for calculation of energetic properties cannot be recommended.

The results for CFF91 are more interesting. Superficially, CFF91 seems to fall among the standard diagonal force fields (AMBER\*, DREIDING, and Alchemy) in accuracy. However, a closer investigation reveals that the largest errors are obtained when calculating halides. For these compounds, CFF91 has to rely on general parameters, which lowers the accuracy substantially. Looking only on cases in which CFF91 can use explicit parameters, it is found to be among the best force fields, with results comparable to MMFF93 and the MM2/MM3-based force fields.

Insight gives no warning messages when the general parameters are used. It is strongly recommended that the output file is checked for this possibility when new systems are calculated.

### MM3

MM3 builds on the classical MM2 concept, but with several extensions and improvements. The intent in the creation of MM3 was to keep the accuracy from MM2 while adding new functionality. Substantial effort has gone into describing the entire low range of the energy hypersurface, thus enabling calculation of vibrational spectra as well as thermodynamic properties. As can be seen from the test results, the accuracy in relative conformational energies is apparently equal for MM3(92) and MM2(91), but with the errors more evenly distributed for MM3.

### CONCLUSIONS

The best possible accuracy obtainable in basic molecular mechanics tasks has not been drastically improved since the 1985 version of MM2. However, the overall level of the currently used force

fields has gone up. Other functional forms have become available that can equal the performance of MM2/MM3 (notably MMFF93 and CFF91), but of those only MMFF93 has a parameter set sufficient to equal the MM2/MM3-based force fields in this test. MM2 can be considered a mature method, whereas rapid development can be seen for MM3,\*\* MMFF,<sup>57</sup> and CFF.<sup>58</sup> Even though the methods tested were the most recent generally available, for several force fields in the study improved versions exists.

Several factors are responsible for different performances of the force field. In decreasing order of importance, we can identify some of them:

1. Accurate and specific parameters. In several cases, use of general or replacement parameters resulted in large inaccuracies. For any calculations, it is important to be aware of the quality of the parameters in use. If the program is set up to utilize estimated parameters without clear warning, it is necessary to scrutinize the actual parameter usage for each case.
2. A good treatment of electrostatic interactions. Specifically, this seems to be what differentiates between the harmonic force fields in the test, with acceptable results for AMBER\* and doubtful values from DREIDING and Alchemy. The poor performance of UFF with charges demonstrates that it is highly important to make the charge model compatible with the underlying force field.
3. Anharmonicity. The seven best force fields in the test, all MM2/MM3-based force fields and MMFF93, have anharmonic stretch and bend terms. They also include at least three terms from the torsional Fourier series.

Going outside the seven best, where the average error is around 0.6 kcal/mol, AMBER\* (with an average error of 0.88 kcal/mol) does not have anharmonic terms (factor 3), and CFF91 (with an overall average error of 1.08 kcal/mol) lacks certain specific parameters (factor 1). Note that if the halides are excluded, the average error of CFF91 is halved. Other factors, which may be important in specific cases but have not been fully tested here, include the number of nondiagonal terms and the treatment of conjugated systems.

\*\*MM3(94); see ref. 4b.

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